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BEFORE THE BOARD OF PATENT APPEALS
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Appellant(s): Newman, *et al.*

Philip M. Goldman
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed 7/20/95.

(1) *Status of claims.*

The statement of the status of claims contained in the brief is correct.

(2) *Status of Amendments After Final.*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(3) *Summary of invention.*

The summary of invention contained in the brief is correct.

(4) *Issues.*

The appellant's statement of the issues in the brief is substantially correct. The rejection of claims 2-8 under § 103 in view of Chen and Galfre` has been withdrawn in the instant Examiner's Answer. Likewise, the rejection of claims 9-10 under § 103 in view of Chen is also withdrawn.

(5) *Grouping of claims.*

Applicants argue the following points.

a. Applicants urge that the claims stand or fall together. This is not agreed with. The claims at issue are rejected under two different sections of title 35 U.S.C., § 112, first paragraph and §§ 102/103, respectively. In other words, the first issue is whether or not the invention as claimed is taught by the prior art. The second issue is whether the combination of the references render the claimed invention obvious. This issue is separate from the first issue because the interpretation of the claims is not at issue here as in the previous claims. Furthermore, the honorable Board's attention is directed to the fact that claim 3, and all the claims which depend from claim 3, do not recite the limitation concerning any sort of allosteric binding mechanism whatsoever. Finally, the third issue is whether the specification as filed has clearly taught how to make and use the full scope of the invention as claimed, assuming *arguendo* that applicants have taught how to make and use a single, preferred allosteric antibody, that does not necessarily constitute a teaching of all allosteric antibodies which could possibly be made. This third issue is separate from the first two because the factors of the state of the art, the predictability of the art and the presence or absence of any working examples all affect whether applicants have enabled the full scope of the invention. Accordingly, for at the least the foregoing reasons, the claims do no stand or fall together because the different rejections are on different grounds.

(6) *Claims appealed.*

The copy of the appealed claims contained in the Appendix to the brief is substantially correct. Claim 8 in the copy of the claims still recites dependency from itself. Originally, the claims were filed without a claim 8. In the first action on the merits, claims 9-11 were renumbered 8-10 pursuant to Rule 126. However, renumbering claim 9 as claim 8 lead to claim 8 depending on itself. Consequently, pending claim 8 was presumed to depend from claim 7 and was examined as such. No comments were received from applicants and accordingly, the current examination continues to with this interpretation.

(7) *Prior Art of record.*

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

a. Smolka *et al*, Gastroenterology, vol. 98(3):607-614, 1990

b. Galfre' *et al*, Methods of Enzymology, vol. 73:3-46, 1981

c. Ellis *et al*, 4,447,528 May 8, 1984

(8) *New prior art.*

A new reference has been cited in support of the examiner's position in response to the arguments of the rejections under § 112, § 102, and § 103.

Roitt *et al*, Immunology, second ed., J.B. Lippincott Company East Washington Sq. Phil. PA 19105, "Antigen Recognition", pp 7.1-7.6, 1989

(9) *Grounds of rejection.*

The following ground(s) of rejection are applicable to the appealed claims.

1. The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to make and/or use the invention, i.e., failing to provide an enabling disclosure and failing to adequately describe the instant invention.

The specification does not provide an adequate disclosure to enable one of skill in the art to practice the invention commensurate with the scope of the claims. The specification disclose that the antibodies of the invention bind to intrinsic factor and are competitive with vitamin B12 for binding to IF in the "allosteric" sense in that the antibodies cannot be bound to intrinsic factor at the same time vitamin B12 is bound to intrinsic factor. The specification provides data showing the competitive inhibition of the binding of cobalbumin (synthetic

vitamin B12) to intrinsic factor in Fig. 1. Figure 2 purports to show a first order dissociation rate of antibody from intrinsic factor. Applicants urge that the spike and subsequent dissociation in a concentration dependent fashion relates to the competition between the antibody-intrinsic factor in dynamic equilibrium and the B12-intrinsic factor in dynamic equilibrium. Thus, the results of Figure 2 would seem to buttress the conclusion that the 585.3A3A8 antibody merely binds at the binding site to B12-intrinsic factor or in a manner that sterically hinders the binding. Further, the specification does not adequately describe how to obtain and use these antibodies. Applicants have not established that the alleged "allosteric" binding mechanism hypothesized by the specification indeed exists. Further, the specification does not adequately describe how to obtain the antibodies. The previous application merely set forth competitive binding data which was completely inconclusive. Applicants have chosen to interpret these data to mean that the claimed antibody composition has allosteric binding affinity. However, the competitive inhibition data of figure 1 do not support such a conclusion. Figure 2 purports to provide dissociation rate data showing first order dissociation. Additionally, the rate of dissociation is directly proportional to the amount of B12 present in solution. The rate of dissociation in a normal first order rate graph shows a linear

result plotting ln c/c_0 against time. The data provided only show a "relative response" without clearly explaining what this parameter is or to what it is relative. Moreover, the x axis does not show time, it shows "seconds in dissociation phase" which does not provide the requisite time. Therefore, applicant's data do not adequately support the statement in the specification at page 22, line 8, that the dissociation is first order. In view of the foregoing discussion of the insufficiency of the data presented by applicants, the specification fails to teach how to make and use the invention as disclosed.

Applicants have disclosed an invention having a certain activity and are asserting that their invention contains all derivatives that have said certain activity. To support such a disclosure, applicants have provided a single disclosed antibody. Undue experimentation would be required to extrapolate the preferred embodiment to any and all antibodies containing this function because applicants have not provided the routineer with the necessary guidance enabling said routineer to obtain other antibodies having the same binding activity. Considering the fact that applicants have not conclusively established the disclosed activity (ie. allosteric binding activity) for the preferred antibody, adequate guidance clearly does not exist for any antibody containing allosteric binding activity. Accordingly, undue experimentation would be required to practice the invention

as described. See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. Appls. & Int. 1986).

The description on pages 13 and following of the generation of intrinsic factor antibodies is of a relatively generic nature. Specifically, no particular peptide or epitope is set forth that would teach one of ordinary skill in the art how to reproducibly obtain applicant's preferred embodiments. Note, for example, the use of conventional, commercially available reagents at the bottom of page 14, top of page 15. Because of such general disclosure, the specification lacks teaching of the critical elements necessary to produce the preferred 585.3A3A8 as opposed to any other antibody. Without such guidance, the specification is deficient in teaching how to make the invention. Accordingly, deposit is required of applicant's 585.3A3A8 antibody to insure availability and viability. See 37 C.F.R. 1.801-1.809.

2. Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

3. Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Smolka.

The claim is broadly drawn in functional terms to a composition comprising an antibody that binds to an allosteric epitope on intrinsic factor. However, review of the specification to elucidate support for such a claim shows that the

specification only provides competitive binding data. Applicants have chosen to interpret these data to mean that the claim antibody composition has allosteric binding affinity. However, the competitive inhibition data of figure 1 do not support such a conclusion. Figure 2 purports to provide dissociation rate data showing first order dissociation. Additionally, the rate of dissociation is directly proportional to the amount of B12 present in solution. The rate of dissociation in a normal first order rate graph show a linear result plotting ln c/c_0 against time. The data provided only shows a "relative response" without clearly explaining what this parameter is or to what it is relative. Moreover, the x axis does not show time, it shows "seconds in dissociation phase" which does not provide the requisite time. Therefore, applicant's data do not adequately support the statement in the specification at page 22, line 8, that the dissociation is first order. Accordingly, the current rejection is maintained under the conclusion that the specification merely provide data which show competitive binding between B12 and IF.

Smolka disclose polyclonal antibodies to intrinsic factor. The disclosure of Smolka at page 612, first paragraph of the left column shows that the binding of anti-intrinsic factor antibodies bind to IF in a way that "conformationally affect[s]" the reactivity of the other reaction site. See page 619, line 9, left

col.. Since Smolka teaches a antibodies having a binding activity where the antibody can only bind intrinsic factor in the absence of B12, the claims are anticipated.

It is noted that the specification does not actually show the argued embodiments of allosteric binding to intrinsic factor, only competitive binding is disclosed. Note, for example the abstract at line 11 where cobalbumin binding is inhibited by the claimed antibodies. Notice also the teaching in Smolka where five antibodies were capable of inhibiting the binding of Cobalbumin to IF. Therefore, the embodiments are still considered to be met by the prior art and the antibody in the Smolka reference is considered to be the same as applicants'. That evidence is the competitive binding assay set forth in example 6 and figure 1. As concentration of B12 increases, the luminescence decreases. The competitive binding disclosed by Smolka at page 609, top of the left column is the same evidence presented by applicants. Accordingly, the reference is anticipatory.

In addition, applicant's new experiment set forth on page 22 of the instant specification does not overcome the instant rejection under §102 because the supplemental experiment is merely further characterization of the claimed invention. Such an experiment does not serve to distinguish the claimed antibody from the prior art. To completely distinguish their invention from the prior art, applicants are invited to present side-by-

side comparison showing that the binding characteristics of the claimed antibody are different from that of the prior art. Otherwise, no evidence exists of record to show that the prior art antibody would not inherently contain the allosteric characteristics claimed by applicants.

(10) *New ground of rejection.*

This Examiner's Answer contains the following new grounds of rejection.

1. Claims 2-6, 9, and 10 are rejected under 35 U.S.C. § 103 as being unpatentable over Smolka in view of Ellis.

The claims are drawn to a generic method of diagnosis involving anti-intrinsic factor antibodies as well as kits for use in the method of diagnosis. The point of patentability in the instant methods of diagnosis and kits for use therewith is essentially the antibody.

Smolka has been discussed previously.

The Ellis reference teaches a generic method of binding antibody which blocks the binding of intrinsic factor to B12. The limitation of claim 10 to monoclonal antibodies is considered obvious as the generation of monoclonal antibodies from polyclonal antibodies was considered obvious in 1991. Appellant's attention is directed to *Ex parte Ehrlich*, 3 USPQ2 nd 1011 (BPAI, 1987). Accordingly, the claimed diagnostic assay is considered obvious as is the substitution of bound antibody for bound

intrinsic factor. Note especially the teaching in the reference at col. 2, lines 30 and following. The reference teaches the isolation of B12/intrinsic factor complexes from antibody/intrinsic factor complexes. Moreover, the claims also recite more particularly the intrinsic factor attached to a support. The claimed method is merely substitution of an antibody for intrinsic factor on the support. Since the two exist in dynamic equilibrium where constant association dissociation occurs, the substitution of bound intrinsic factor for bound antibody is considered to be an obvious variation.

2. Claims 7 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Smolka in view of Galfre.

Claims 7 and 8 are drawn to generic methods of producing antibodies.

Smolka has been previously discussed.

The Galfre reference provides specific teachings for the production of antibodies for any particular antigen. Note the reference at the beginning of the second paragraph.

It would have been *prima facie* obvious to apply the general technique of Galfre' to the specific antibodies of Smolka. The reason for such a combination is that the technique set forth in Galfre` is essentially a generic technique which is sufficient to generate antibodies against "a large variety of antigens" (c.f. page 3, second paragraph. Given that the technique is effective

against a large variety of antigens, no reasons exist why the technique would not work against IF. This is especially so when the technique is compared to that of Smolka which specifically teaches the production of monoclonal antibodies to intrinsic factor (IF). Consequently, the method of manufacturing monoclonal antibodies in like those of Smolka in the particular method of Galfre` is considered *prima facie* obvious absent evidence to the contrary.

3. Claims 9 and 10 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims currently recite the following at line 12 of claim 9 "...that is released from binding in the presence, wherein the ....". What is supposed to be present? It would appear that appellants are using similar language to that recited in claim 1. Such an interpretation would mean that the presence of B12 is intended. However, the language is not identical and therefore, the meaning of the claims is vague and indefinite.

(11) *Response to argument.*

Applicants argue essentially the following grounds of traversal and believe that if the Board of Patent Appeals and Interferences is in agreement with appellant's interpretation of their experiments, then all the grounds of rejection will fall

and the claims will be in condition for allowance. This is not so. The issues under §§§ 112, 102 and 103 are distinct issues which require separate consideration for the reasons delineated in the grouping of the claims.

a. Appellant's traversal begins with the rejection under § 112. Appellants allege that their antibodies are of the "allosteric competitive" class. This class of antibody is allegedly established by the BIAcore experiment which purports to show the dissociation of intrinsic factor (IF) from the antibody (AB) in a manner which is dependent on the concentration of B12 present in the experiment. Appellants urge that the critical parameter of this experiment is the presence of a flow through cell. In other words, the individual elements do not exist in equilibrium because the medium in which the reaction occurs is flowing or moving. Consequently, appellants conclude that no dynamic equilibrium can exist which would serve to prevent the B12 vitamin from competing with the antibody for the binding of intrinsic factor.

b. In section B. at page 12 of the Brief filed 7/20/95, appellants argue that Smolka does not describe extracting B12 before selecting the hybridomas that secrete antibodies to IF. Consequently, any alleged allosteric antibodies would not be identified.

These arguments are not persuasive for the reasons that follow.

a. The basic problem with the argument set forth in the Brief on Appeal filed 7/20/95 in section A. is that it appears to contradict the basic laws of thermodynamics. Note the Roitt reference in Fig. 7.5 where antibody affinity is described. The antibody affinity is shown to function like any other chemical reaction where a balance or equilibrium exists between the bound and unbound state. Note that the Ab(antibody) and the Ag(antigen) are capable of existing in separately and together. Therefore, logic would dictate that if two binding proteins existed (one antibody and one vitamin B12) rather than just one, that the binding protein with the greater affinity for the antigen would bind the antigen in greater percentage. This sort of behavior is typical in chemistry and biology.

The bearing this behavior has on the rejections of the instant case is as follows. Applicants have not explained how the BIAcore experiment set forth in fig. 2 of the instant application works to eliminate the basic law of chemical equilibria set forth above. Such a basic law is canonical and provides a legitimate scientific basis to doubt the enablement of the invention as claimed. It is submitted that applicant's position purports to violate the basic law without any other basis than the arguments of

applicant's representative. It is respectfully submitted that arguments of counsel are not substitute for hard evidence.

Finally, another plausible explanation exists which would explain the results set forth in fig. 2 and which render the invention obvious as claimed. This explanation is that both B12 and the preferred antibody compete for the same spot on intrinsic factor (IF). The results of fig. 2 show a gradually increasing rate of dissociation of IF from the bound antibody. In terms of Fig. 7.5 of Roitt, the experiment represents the step-wise addition of B12 to for the three way formula where Ag is IF:

Ab + IF <-> AbIF + IFB12 <-> IF + B12

In the experiment of fig. 2, the concentrations of Ab and IF are constant and applicants are steadily adding more B12. It stands to reason that more B12 will drive the reaction to formation of more B12IF complexes, especially if B12 binds IF with greater affinity than Ab. Such a result would result in faster dissociation of IF from Ab in the BIAcore experiment because there is a greater concentration of B12 to compete with Ab in the reaction above.

In addition, the selection assays described in the specification at pages 19 and following do not permit the discrimination of antibodies which bind allosterically, and

consequently are the subject of appellants alleged invention and antibodies which compete in a competitive sense. The screening experiments set forth would yield the same results for both the competitive and allosteric inhibition. The ability to distinguish between the two is critical because appellants argue that their invention is drawn exclusively to the allosteric form of inhibition. Furthermore, appellants have not deposited the exemplified antibody. Thus no standard for comparison exists within the specification. Therefore, on of ordinary skill in the art could not produce the claimed antibodies without the practice of undue experimentation due to the generic nature of the screening procedures, the lack of deposit of a representative antibody or hybridoma, and the lack of binding epitope characterization.

Such a scenario is essentially the basis for most of the art rejections. The art rejections rely on the analysis of the preceding paragraph. Such an analysis interprets the data of fig. 2 as corollary to the competitive binding data of fig. 1. Such data teaches one of ordinary skill in the art that the preferred antibody and the prior art antibodies of Smolka have the same function. That function is the ability to interrupt or compete for the binding of IF with B12. Note the Smolka reference at page 612, left col., first

paragraph, for example. At this passage, Smolka clearly teaches polyclonal antibodies which block formation of the IF-Cbl complex (Cbl is cobalbumin which is another name of vitamin B12). Therefore, with regard to the broadest claims, the function of binding to IF only in the absence of B12 is met by the teaching of Smolka.

In closing, it is noted that applicant's Brief, filed 7/20/95, does not appear to respond substantively to the outstanding arguments surrounding the scope of the invention as claimed and the necessity of the deposit. Both issues were argued in the first and subsequent actions on the merits.

b. These arguments of section B. are not persuasive because the claim is not limited to allosteric antibodies. The claim recites the functional limitation that the antibody should bind IF only in the absence of B12. Binding is released only in the presence of B12 and upon the binding of B12 to IF. If the two molecules bind the same site, this will occur. As B12 binds to the IF binding site, then the antibody will no longer be able to bind at that same site. Consequently, the antibody will bind to IF only in the absence of B12, ie. when B12 cannot compete with the antibody, and the antibody will be released upon binding of B12 to IF because the B12 will compete for the binding site

with the claimed antibody. Consequently, appellant's arguments apply equally to competitive antibodies as well as allosteric antibodies.

Furthermore, the reference does teach at page 619, left col., that one binding site conformationally affects another binding site. Consequently, assuming *arguendo* that the claims are interpreted as limited to allosteric antibodies. The claims essentially encompass any allosteric binding mechanism. Since an allosteric binding mechanism is essentially one which involves the change in shape or "conformation" as a result of binding, such a mechanism is taught by the Smolka reference. Accordingly appellant's arguments are not persuasive.

1. The arguments of sections C. and D. at pages 13 and 14 of the 7/20/95 Brief are moot in view of the new grounds of rejection set forth in the present Examiner's Answer.

(12) *Period of response to new ground of rejection.*

In view of the newly cited art, appellant is given a period of TWO MONTHS from the mailing date of this examiner's answer within which to file a reply to any new ground of rejection. Such reply may include any amendment or material appropriate to the new ground of rejection. Prosecution otherwise remains closed. Failure to respond to the new ground of rejection will result in dismissal of the appeal of the claims so rejected.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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